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<b>(21) International Application Number:</b> PCT/EP95/01801 <b>(22) International Filing Date:</b> 12 May 1995 (12.05.95) <b>(30) Priority Data:</b> 94201434.1 20 May 1994 (20.05.94) EP <b>(34) Countries for which the regional or international application was filed:</b> AT et al. <b>(71) Applicant (for all designated States except US):</b> JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> JANS, Eugene, Marie, Jozef [BE/BE]; Rodekruislaan 3, B-2450 Meerhout (BE). GILIS, Paul, Marie, Victor [BE/BE]; Schransdriesstraat 14, B-2340 Beerse (BE).		<b>(81) Designated States:</b> AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> CHEWABLE FLUBENDAZOLE TABLETS FOR COMPANION ANIMALS		
<b>(57) Abstract</b>  The present invention relates to compositions comprising flubendazole of formula (I), which are palatable to companion animals, especially dogs. These find utility as palatable anthelmintic compositions for the treatment of helminthiasis. <div style="text-align: center; margin-top: 20px;"> <chem>COC(=O)Nc1nc2cc(ccc2n1)C(=O)c3ccc(F)cc3</chem> </div> <div style="text-align: right; margin-top: -20px;"> <b>(I)</b> </div>		

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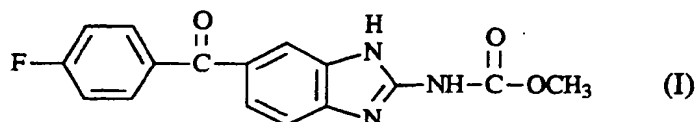
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## Chewable flubendazole tablets for companion animals

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The present invention relates to compositions comprising flubendazole, which are palatable to companion animals, especially dogs. These compositions find utility as palatable anthelmintic compositions for the treatment of helminthiasis.

Flubendazole is an anthelmintically active compound having the formula (I).



15

Flubendazole is the generic name of methyl [5-(4-fluorobenzoyl)-1H-benzimidazol-2-yl]carbamate. Flubendazole has been described in US-3,657,267. Methods of preparing said compound are also mentioned in said patent. The anthelmintic activity has already been described extensively and the product has been on the market for many years as a veterinary pharmaceutical under the brand names Flubenol®, Biovermin®, Flubenol KH®, Flumoxal®, Flutelmium®.

Over the years, owners of companion animals and veterinarians have continually made the remark that the available tablets, pills or formulated compositions marketed for admixture of flubendazole with feeds are not completely satisfactory. This has resulted in the reluctance of the animals to ingest said tablets, pills or feed containing medication. It would therefore be highly advantageous and most desirable if flubendazole could be rendered palatable without destroying its efficacy. Furthermore, it would be most advantageous if a palatable composition containing flubendazole could be prepared in the form of a chewable tablet, pill, granulated product or the like, especially a chewable tablet.

It is therefore an object of this invention to provide palatable, therapeutically effective compositions containing flubendazole, useful for the treatment of helminthiasis in companion animals, especially dogs.

It is also an object of the present invention to provide methods for preparing compositions containing flubendazole which are palatable for companion animals, especially dogs.

- 5 Compositions according to the present invention will preferably comprise besides active ingredient pharmaceutically acceptable carriers and excipients, such as fillers e.g. lactose, sucrose, mannitol, maize starch, microcrystalline cellulose or calcium hydrogen phosphate; lubricants e.g. stearic acid, polyethylene glycol, magnesium stearate, talc or silica; disintegrants e.g. rice, potato or maize starch, sodium starch glycollate or
- 10 croscarmellose sodium (croscarmellose sodium is the British Approved Name for crosslinked carboxymethylcellulose); binding agents e.g. pregelatinised maize starch, polyvinylpyrrolidone or hypromellose (hypromellose is the British Approved Name of hydroxypropyl methylcellulose) and wetting agents.

- 15 The compositions of the present invention always contain large amounts of brewer's yeast.

Brewer's yeast throughout this application means in fact the product of the autolysis and hydrolysis of brewer's yeast. Said autolysed and hydrolyzed product can, for instance,

20 be obtained in the following manner. *Saccharomyces cerevisiae* used in breweries is separated after the brewing process from the residual grain. Said yeast is first heated and pumped into an autolysis tank. During the autolysis the yeast's own enzymes break down the cell wall as well as the yeast proteins. After said autolysis the yeast is again heated to inactivate any remaining enzymes. Following the inactivation the yeast is

25 centrifuged to collect the cell wall material. Said cell wall material is then pasteurized and spray dried, after which the product is completely hydrolyzed with hydrochloric acid and then neutralized with sodium hydroxide. The remaining product is then again pasteurized and spray dried.

- 30 Interesting fillers are lactose, sucrose or microcrystalline cellulose; preferably lactose and microcrystalline cellulose. Interesting lubricants are stearic acid, polyethylene glycol, hydrogenated vegetable oil, sodium stearyl fumarate or magnesium stearate, preferably magnesium stearate. Interesting disintegrants are rice, potato or maize starch, preferably croscarmellose sodium. Preferred binding agent is hypromellose. Several grades of
- 35 hypromellose are available. Preferred grade of hypromellose is hypromellose 2910 15 cps (The grades of hypromellose are distinguished by a four digit code, here 2910. The first two digits represent the approximate percentage composition of methoxyl groups,

-3-

and the third and fourth digits the approximate percentage composition of hydroxypropyl groups. The indication "15 cps" refers to the viscosity of 15 centipoise (15 mPa.s) of a 2 % solution measured at 20 °C.

- 5 Interesting compositions contain from 20% to 40% by weight of active ingredient, more interesting compositions comprise about 21% up to 35% by weight of the active ingredient. Preferably the active ingredient is present in about 22% by weight.

- 10 Brewer's yeast is present in amount from 40% to 70% by weight. Interesting compositions comprise from 45% to 70% by weight of brewer's yeast. Preferably the brewer's yeast is present in about 50% by weight.

A binder may be absent or may be present up to an amount of 4%. Preferably, the binder is hydroxypropyl methylcellulose in an amount of about 2.5%.

15

Fillers may be absent or present in an amount up to 25%. Preferably said filler is a carbohydrate derivative such as sorbitol or cellulose, especially microcrystalline cellulose. Mixtures of said carbohydrate derivatives may also be present.

- 20 Wetting agents may be absent or present in an amount up to 0.5% by weight. Preferred wetting agent is sodium lauryl sulphate.

Lubricants are present in an amount from 0.1% to 1.5% by weight. Preferred lubricant is magnesium stearate.

25

Flavouring agent may be present in an amount from 0.001% to 0.5 % by weight. Said flavouring agents are commercially available. Preferred flavouring agents are meat flavours. Meat flavours are commercially available as additives for pet feed.

- 30 Interesting compositions comprise by weight based on the total weight of the composition.

- |    |                   |   |                     |
|----|-------------------|---|---------------------|
|    | flubendazole      | : | from 20% to 40%     |
|    | brewer's yeast    | : | from 40% to 70%     |
| 35 | fillers           | : | from 0% to 25%      |
|    | binding agents    | : | from 0% to 4%       |
|    | flavouring agents | : | from 0.001% to 0.5% |

-4-

wetting agents : from 0% to 0.5%  
 lubricants : from 0.1% to 1.5%

5 More interesting compositions comprise by weight based on the total weight of the composition.

flubendazole : from 21% to 35%  
 brewer's yeast : from 45% to 70%  
 fillers : from 0% to 25%  
 10 binding agents : from 0% to 4%  
 flavouring agents : from 0.001% to 0.5%  
 wetting agents : from 0% to 0.5%  
 lubricants : from 0.1% to 1.5%

15 Preferred compositions comprise by weight based on the total weight of the composition.

flubendazole : from 22% to 33%  
 brewer's yeast : from 50% to 65%  
 hydroxypropyl methylcellulose : from 2 % to 3%  
 20 flavouring agents : from 0.1% to 0.2%.

The compositions may be prepared by intimately mixing the ingredients.

25 One way of preparing the compositions according to the invention is to blend flubendazole with the suitable excipients and to granulate said blend.

According to the present invention the composition is in the form of a tablet, preferably a chewable tablet.

30 Tablets according to this invention may be right circular cylinders, the end surfaces of which may be flat or convex and the level edged. Said tablets may have lines or break-marks and may bear a symbol or other markings.

The tablets according to the present invention also should have an appropriate strength.  
 35 An appropriate strength is defined as exceeding 100 N (Newton). Said tablets have a thickness of about 4.5 mm.

The tablets of the present invention are preferable packaged in impermeable package, e.g. Tristar, which is a laminate van polyvinyl chloride, polyethylene and polyvinylidene  
 40 chloride.

As is shown in example 3 hereinunder almost 90 % of the dogs (of different breeds) readily accepted the tablets of the above composition.

5 A further aspect of the present invention provides a method of treating companion animals, especially dogs suffering from helminthiasis which comprises the administration of a chewable tablet containing flubendazole.

It will be appreciated that the precise therapeutic dose of the active ingredient will depend on the age and the condition of the animal and the nature of the condition to be treated and will be at the ultimate discretion of the attendant veterinary.  
10

However, in general effective doses of the treatment of helminthiasis in companion animals, will lie in the range of 5 mg/kg to 50 mg/kg body weight.

#### Example 1

##### 15 Preparation of the binder solution

150 g of Hypromellose 2910 15 cps and 18 g of sodium lauryl sulphate were dissolved in 3400 ml demineralized water under stirring.

##### Preparation of the granulate

20 1.320 g of flubendazole, 60 g colloidal silicon dioxide en 3002 g brewer's yeast are mixed in a fluidized-bed granulator until a homogenous mixture is obtained. Subsequently, the binder solution is sprayed onto the powder mixture during continued mixing. After the spraying the granulate is dried with an inlet air temperature being  
25 75°C.

##### Preparation of the compression mixture

The dried granulate, 750 g microcrystalline cellulose, 660 g of crystalline sorbitol and 30 g of magnesium stearate are sieved and are mixed in a planetary powder mixer until a  
30 homogenous mixture is obtained.

##### Preparation of the tablets

From the above compression mixture tablets of 1000 mg are prepared using a rotatory tablet press.

##### 35 Example 2

According to analogous processes as mentioned above the following tablets were prepared.

composition	A	B	C	D	E
ingredient	quantity (in mg)	quantity (in mg)	quantity (in mg)	quantity (in mg)	quantity (in mg)
flubendazole	330.0	330.0	220.0	220.0	220.0
brewer's yeast	616.3	500.0	577.9	500.4	500.4
colloidal silicon dioxide	-	-	9.5	10.0	10.0
hypromellose 2910 15 cps	-	-	23.8	25.0	25.0
sodium laurylsulphate	-	2.9	2.9	3.0	3.0
sorbitol crystalline	-	-	105.0	110.0	110.0
sorbitol 70%	-	107.2	-	-	-
meat flavour	0.5	0.5	1.5	1.6	1.6
magnesium stearate	3.3	9.5	9.5	10.0	5.0
microcrystalline cellulose	-	-	-	120.0	125.0
total weight of the tablet	950.0	950.0	950.0	1000.0	1000.0

### Example 3

A total number of 119 dogs of 40 different breeds with body weights ranging from 5 to 80 kg (average 27 kg) were used in this experiment. The tablets used in this experiment had composition E (see example 2). In 66 dogs (55%) the time of administration of the tablets had no connection with the meal. From the remaining 53 dogs, 38 were treated before meal, 2 dogs during their meal and 13 dogs got the tablets after their meal. In 68 dogs the usual diet consisted of only 1 type of food : either canned food (31 dogs), or dry food in different kinds of presentations (16 dogs), or home prepared meal (21 dogs). The diet of the remaining 51 dogs was of mixed nature : canned and dry food (3 dogs), canned and home prepared meal (23 dogs), dry and home prepared meal (24 dogs) and canned, dry and home prepared meal (1 dog). 103 dogs (86.5%) accepted the flubendazole tablets readily whereas 16 dogs (13.5%) refused the tablets. The palatability was not connected with the breed, the composition of the diet or the time of administration of the flubendazole chewable tablets.



# Claims

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1. An anthelmintic composition palatable to companion animals which comprises  
5        flubendazole and brewer's yeast.
2. A composition according to claim 1 wherein said companion animals are dogs.
3. A composition according to claim 1 wherein the amount of brewer's yeast ranges  
10        from 40% to 70%.
4. A composition according to claim 1 comprising by weight based on the total weight of  
the composition :

flubendazole	:	from 20% to 40%
15        brewer's yeast	:	from 40% to 70%
fillers	:	from 0% to 25%
binding agents	:	from 0% to 4%
flavouring agents	:	from 0.001% to 0.5%
wetting agents	:	from 0% to 0.5%
20        lubricants	:	from 0.1% to 1.5%
5. A composition according to claim 4 comprising by weight based on the total weight  
of the composition :

flubendazole	:	from 22% to 33%
25        brewer's yeast	:	from 50% to 65%
hydroxypropyl methylcellulose	:	from 2 % to 3%
flavouring agents	:	from 0.1% to 0.2%.
6. A composition according to claim 5 wherein said composition is in the form of a  
30        chewable tablet.
7. A chewable tablet according to claim 6 wherein said tablet has the following  
composition :

flubendazole	:	220.0 mg	22.00%
35        brewer's yeast	:	500.4 mg	50.04%
colloidal silicon dioxide	:	10.0 mg	1.00%
hypromellose 2910 15 cps	:	25.0 mg	2.50%

-8-

	sodium lauryl sulphate	:	3.0 mg	0.30%
	sorbitol crystalline	:	110.0 mg	11.00%
	meat flavour	:	1.6 mg	0.16%
	magnesium stearate	:	5.0 mg	0.50%
5	microcrystalline cellulose	:	125.0 mg	12.50%

8. A process of preparing a composition according to claims 1 to 7 wherein flubendazole is intimately mixed with the excipients.

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9. Use of a composition as claimed in claim 1 for the manufacture of a medicament for treating companion animals suffering from helminthiasis.

10. Use as claimed in claim 9 wherein said companion animals are dogs.

## INTERNATIONAL SEARCH REPORT

 Intern. Application No  
 PCT/EP 95/01801

 A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K9/00 A61K9/20 A61K31/415 A23K1/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 007 no. 095 (C-163) ,23 August 1983 & JP,A,58 021615 (FUJISAWA YAKUHHN KOGYO KK) 8 February 1983, see abstract & DATABASE WPI Week 8311 Derwent Publications Ltd., London, GB; AN 83-26659 & JP,A,58 021 615 (FUJISAWA PHARM. KK) , 8 February 1983 see abstract ---	1-3,6,9, 10
Y	GB,A,2 055 575 (AMERICAN CYANAMID CO.) 11 March 1981	1-3,6,9, 10
A	see page 1, right column - page 2, left column; claims 1,2; examples 4-8 ---	4,5,7
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 320 320 (SO.GE.VAL. S.A.) 14 June 1989 see column 1-2; claims 1,4,6-9 ---	1-3,6,9, 10
A	DE,A,944 581 (ZELLSTOFFFABRIK WALDHOF) 15 December 1955 see page 1 -----	1,3,6,8

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/01801

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		DE-A-	3028082	19-02-81
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